Neuroblastoma is an important cancer of children, the therapy for which leaves much to be learned. It is a unique tumor in several respects. It is most common in early infancy; it has an impressive history of spontaneous regression, and its natural history is highly predictable when age of the patient, histopathologic classification and accurate clinical staging are considered.

It apparently has specific cellular antigenic components, and, like some trophoblastic tumors, it secretes characteristic metabolic products which can provide "markers" permitting detection of residual tumor following operation, occult metastasis, or early recurrence.

Finklestein and Gilchrist stress the importance of a complete patient evaluation before therapy, from which a multidisciplinary treatment plan can be developed. They propose "second look" surgical operation after a significant tumor-free interval, and they raise the intriguing possibility of immunotherapy for this tumor. They also wisely point out the special insights and experience required of radiation therapists who treat infants and children.

Their review places in perspective a cancer which demands the concerted skills of pathologist, bio-chemist, immunologist, radiologist, surgeon, radiation therapist, pediatric oncologist and family physician. The review presents lessons for all of these disciplines and for geneticists and embryologists as well.

During the past decade, substantial progress in treatment of childhood cancer has been made. The most favorable treatment programs for acute leukemia are expected to produce median survival of over four years, and apparent "cures" are being referred to with increasing confidence. Similarly, with childhood solid tumors the co-ordination of more aggressive, multidisciplinary therapeutic plans is leading to prolonged tumor-free survival and improved cure rates.

These encouraging results are not being obtained solely because of new therapeutic discoveries, nor are they being obtained by all who treat children with cancer. They are being seen at institutions where basic and clinical investigators have developed sophistication in combining their best skills and have systematically applied many pieces of useful information that have been gathered painstakingly from careful investigation.

Thus, while several years ago it mattered little where or by whom a child with cancer was treated, it has begun to matter a great deal. A child with a tumor now deserves evaluation by a team representing all of the disciplines that may have a role in developing the best therapeutic plan.

An appropriate evaluation of a child with a tumor and the development of an individualized plan of therapy will involve accurate histopathologic classification, clinical staging of extent of involvement, and often bio-chemical, immunologic, and isotopic examinations. The contributions to therapy and the appropriate timing of surgical operation, radiation therapy, chemotherapy and, soon, immunotherapy, must all be weighed in developing an optimal therapeutic plan. Moreover, the requirements for teamwork and co-ordination continue as the plan is carried out and new problems arise which also require varied skills.

Institutions expecting to provide good care for children with tumors should have such teams. Institutions that do not establish such teams should refer patients with cancer to those that do. Such teams are necessary to provide the multidisciplinary interaction that can now produce good outcome for some cancers. Patients with tumors which are refractory to current treatments, also should be referred to such institutions, since the accumulation of experience through co-ordinated multidisciplinary investigation provides the greatest opportunity for substantial improvement of current treatments that are still not good enough.

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Lymphocyte Tissue Culture In Transplant Surgery

TO USE LYMPHOCYTE or leukocyte tissue culture in the monitoring of human transplants is to apply a laboratory technique with many potential pitfalls in both interpretation and quantitation[1] to a complex clinical situation. Nevertheless, using this technique, it is often possible to gauge *in vitro* the prevailing immunological trends in a given transplant patient. Unfortunately, in a possible rejection period where time is at a premium, with the method currently in use it takes days to get an answer.

Looking at the overall picture, one is encouraged by the report of Bach et al,[2] in which a good correlation was noted between the results of mixed lymphocyte cultures in 36 patients before operation, and function of their renal transplants after one or two years. None of the patients with a creatinine clearance over 70 ml per minute had originally had more than 5 percent transformed cells in their cultures. Kidney allograft survival in mongrel dogs has been similarly studied by Kisken and Malek.[3]

Lymphocytes taken from a patient satisfactorily suppressed have been variously and contradictorily reported to respond normally *in vitro* or to have diminished responsiveness. Heine et al[4] found that the depression of response to phytohemagglutinin was only insignificantly lower in a group of 30 patients being treated with 6-mercaptopurine or azathioprine when compared with a group of 54 normal controls. Joseph similarly found no change in lymphocyte response to phytohemagglutinin during rejection episodes.[5] However, most other workers have found that patients with a satisfactory level of immunosuppression have a reduced phytohemagglutinin response and that a return to normal responsiveness *in vitro* heralded a rejection crisis or a deterioration in renal function.[6,7,8]

Preceding rejection episodes there also appears to be an increased traffic in the blood of activated lymphocytes similar to that associated with vaccination or virus infection. This is readily detected either by counting atypical mononuclear cells in the peripheral blood, or by measuring the increased rate of RNA synthesis in peripheral blood mononuclears in a two-hour culture.[9] Both of these approaches have the merit of giving prompt answers. The presence of activated cells in the circulation is also reflected in an increased rate of spontaneous transformation in leukocyte cultures.[8,10,11]

Having detected increased immunological activity in a transplant patient, one is faced with the question, is this a desirable response to a pathogenic microorganism or a prelude to rejection? One is hard put to know unless some immunological specificity is introduced into the culture system such that an increased responsiveness of the patient's lymphocytes to the antigens of the allograft can be measured. This object would probably best be achieved by using serial mixed cultures along the lines of those reported by Oppenheim et al,[12] who clearly demonstrated a temporarily enhanced response coincident with episodes of skin graft rejection. Liquid nitrogen banking of viable lymphocytes taken from the donor at the same time as the allograft presents no major technical problems.[13]

Apart from changes in the lymphocyte population in the blood before rejection episodes, there is also a change in the serum level of α_2 globulin, a lymphocyte inhibiting protein. The latter has been reported to be elevated to the point where serum taken from renal transplant patients during rejection episodes causes a decrease in thymidine uptake by lymphocyte cultures.[14] The variable content of patient's serum in cultures of his lymphocytes along with technical variation in the preparation of his cells might explain some of the contradictory reports on responsiveness to phytohemagglutinin.

Lymphocyte tissue culture has wide application in clinical studies,[15,16] and one of its more useful applications may be in the monitoring of transplant patients.

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Water Intoxication in a Beer Drinker

BEER PRODUCES A NUMBER of well known physiologic effects, including a water diuresis which is due to an inhibition of anti-diuretic hormone (ADH) release by both the alcohol[1] and the water contained in beer, and a central nervous system intoxication which is ordinarily due only to the alcohol. Elsewhere in this issue of CALIFORNIA MEDICINE, Gwinup et al report the (fortunately) uncommon association of beer ingestion and water intoxication.

A 46-year-old man with a history of having drunk 3 to 6 liters of beer daily for many years presented to the hospital with mental confusion on three separate occasions over a three-year period, and on each occasion he was found to have significant hyponatremia. Serum osmolality was low, demonstrating dilution of total extracellular solutes by water, and urine osmolality was quite high, indicating inappropriate ADH release; however, preliminary study failed to reveal any of the recognized causes of inappropriate ADH release.[2] If it is assumed that the patient ordinarily tolerated his large daily beer intake without suffering water intoxication, the most likely diagnosis is intermittent or temporary inappropriate ADH release of uncertain cause.

An attempt was made, in the present case, to assess the role played by the ingestion of 5 liters of beer a day, by comparing the effects of one week of beer ingestion, one week of an equivalent amount of water ingestion, and one week of concentrated alcohol ingestion (about 220 grams a day, the amount present in 5 liters of 4.6 vol% beer). Beer ingestion was accompanied by a rising urine osmolality as well as progressive weight gain and hyponatremia which abated abruptly when beer was discontinued. Water ingestion was accompanied by a very slowly falling urine osmolality, as well as some water retention and hyponatremia which abated as the urine gradually became very slightly hypotonic during the last few days of water ingestion. Alcohol ingestion apparently failed to produce either a hypotonic urine or a detectable change in water balance. The authors concluded that beer, per se, may have produced the inappropriately concentrated urine, but allowed for the possibility that the different effects observed between beer ingestion and water ingestion may not have been related to any such effects of beer independently of its water content. What makes the latter possibility attractive is that an abnormality of ADH release, not dependent on beer intake, is strongly suggested by the apparent failure of water or alcohol to result in the production of maximally dilute urine. Furthermore, as was mentioned, the patient may well have tolerated large beer loads on many occasions outside the hospital without developing water intoxication. For these reasons, it seems not unlikely that a non-osmotic factor other than beer—for example, acute anxiety, unusual excitement, abrupt increase in tobacco use, and certain drugs[2]—is causing intermittent and variable release of ADH which resulted in the patterns observed during the periods of study, and which, out of hospital, resulted in water intoxication whenever sufficiently large amounts of water, in the form of beer, also happened to have been ingested. If this interpretation is correct, the role played by beer in the present case is well summarized by the motto appearing on the label of the test beer employed by the authors—"It's the Water."

Finally, although the association of excessive beer intake and water intoxication is certainly an oddity, the present case should serve as a reminder of an entity which, in all likelihood, is not an oddity—that is, temporary inappropriate ADH release, excessive "free-water" intake, and water intoxication.

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